Scientific research article / https://doi.org/10.15446/rcciquifa.v52n3.111080

Acute effect of pregabalin on depressive- and anxiety-like behaviors in adult rats in a pharmacologic model of depression

Alberto Casas Lucich[1a*], Antony Brayan Campos Salazar[2b], Victor Vasquez Matsuda[3c], Karla Masiel Yndigoyen Cueva[2d], José Salvador Carrillo[3e], Giancarlo Ojeda Mercado[1f]

[1] Escuela de Post-grado, Universidad Peruana Cayetano Heredia, Av. Armendáriz 445, Miraflores, Lima, Perú, 15074.

[2] Departamento de Bioquímica, Facultad de Farmacia y Bioquímica, Universidad Nacional Mayor de San Marcos, Jirón Huanta 1182, Lima, Perú, 15001.

[3] Escuela Profesional de Medicina Humana, Universidad Privada San Juan Bautista, Ex Hacienda Villa, Av José Antonio Lavalle N° 302, Lima, Perú, 15067.

E-mail addresses: [a] alberto.casas@upch.pe, [b] antonybcampos@gmail.com, [c] victorgb2009@gmail.com, [d] karla.yndigoyen@unmsm.edu.pe, [e] jose.salvador@upsjb.edu.pe, [f] giancarlo.ojeda@upsjb.edu.pe

[*]Corresponding author: Telephone: +51 921 218 696, E-mail: alberto.casas@upch.pe

Received: September 12, 2023
Corrected: November 7, 2023
Accepted: November 14, 2023

Summary

Introduction: Due to lack of effective and fast-acting therapy, depression can become a life-threatening condition if not treated adequately. In fibromyalgia animal models, pregabalin has shown antidepressant properties. Compared to fluoxetine, the unusual fast-acting antidepressant properties of pregabalin offers the possibility to explore this GABA analogue in the context of depression. **Objective:** we evaluated the acute effect of pregabalin in a reserpine-induced animal models of depression. **Method:** rats were organized into four groups regarding their planned drug regimen: control (C), reserpine (R), reserpine + fluoxetine (RF) and reserpine + pregabalin (RP). The C group received only saline throughout the study. Depressive and anxiety-like behavior were tested using the force swimming test (FST) and the open field test (OFT), respectively. **Results:** Our data shows that both RP and RF groups have a significant longer mobility time (seconds) than the C group during the FST (RP: 44.76 ± 8.37 and RF: 65.86 ± 34.10 vs C: 21.80 ± 11.10, $p<0.05$ for both). No significant differences were observed in immobility time and climbing across all groups ($p>0.05$). On the other hand, RF and RP groups showed a reduced time spent in the center of the arena compared to control ($p<0.05$) in

OFT, suggesting increased anxiety-like behavior. **Conclusion:** Our results show that pregabalin has an acute effect on depressive and can also acutely exert an unexpected anxiety-like behavior as well. Our work reveals an unexpected outcome in the search for fast-acting antidepressants.

Keywords: Reserpine; pregabalin; depression; anxiety; animal model.

Resumen

Efecto agudo de la pregabalina sobre los comportamientos tipo depresivo y ansioso en ratas adultas en un modelo farmacológico de depresión

Introducción: Debido a la falta de un tratamiento eficaz, el trastorno depresivo puede ser riesgoso para la vida si no es tratado adecuadamente. En modelos animales de fibromialgia, la pregabalina ha demostrado propiedades antidepresivas. En comparación con la fluoxetina, la inesperada acción antidepresiva aguda de la pregabalina ofrece la posibilidad de explorar este análogo del GABA en el contexto de la depresión. **Objetivo:** evaluar el efecto agudo de la pregabalina en un modelo animal de depresión inducida por reserpina. **Método:** las ratas fueron agrupadas en cuatro grupos según su régimen terapéutico: control (C), reserpina (R), reserpina + fluoxetina (RF) y reserpina + pregabalina (RP). El grupo C recibió sólo solución salina durante el estudio. Los comportamientos tipo depresivo y ansioso fueron evaluados mediante la prueba de nado forzada (PNF) y la prueba de campo abierto (PCA), respectivamente. **Resultados:** Nuestros datos mostraron que tanto el grupo RP como el RF tienen un tiempo de movilidad significativamente mayor que el grupo C durante la PNF (RP: 44,76s ± 8,37 y RF: 65,86s ± 34,10 vs C: 21,80s ± 11,10, $p<0,05$ para ambos). No se observaron diferencias significativas en el tiempo de inmovilidad y escalada entre los grupos ($p>0,05$). Por otro lado, en la PCA, los grupos RF y RP mostraron una reducción del tiempo en el centro de la arena en comparación con el control ($p<0,05$), lo que sugiere un mayor comportamiento tipo ansioso. **Conclusión:** Nuestros resultados sugieren que la pregabalina tiene un efecto agudo sobre los comportamientos tipo depresivo y ansioso.

Palabras clave: Reserpina; pregabalina; depresión; ansiedad; modelo animal.

Resumo

Efeito agudo da pregabalina nos comportamentos depressivos e ansiosos em ratos adultos em um modelo farmacológico de depressão

Introdução: Devido à falta de terapia eficaz e de ação rápida, a depressão pode tornar-se uma condição potencialmente fatal se não for tratada adequadamente. Em modelos animais de fibromialgia, a pregabalina demonstrou propriedades antidepressivas. Em comparação com a fluoxetina, as propriedades antidepressivas incomuns de ação rápida da pregabalina oferecem a possibilidade de explorar este análogo do GABA no contexto da depressão. **Objetivo:** avaliamos o efeito agudo da pregabalina em modelos animais de depressão induzidos por reserpina. **Método:** os ratos foram organizados em quatro grupos quanto ao regime medicamentoso planejado: controle (C), reserpina (R), reserpina + fluoxetina (RF) e reserpina + pregabalina (RP). O grupo C recebeu apenas solução salina durante todo o estudo. Os comportamentos depressivos e ansiosos foram testados por meio do teste de natação forçada (FST) e do teste de campo aberto (OFT), respectivamente. **Resultados:** Nossos dados mostram que ambos os grupos RP e RF apresentam um tempo de mobilidade (segundos) significativamente maior do que o grupo C durante o FST (RP: 44,76 ± 8,37 e FR: 65,86 ± 34,10 vs C: 21,80 ± 11,10, $p<0,05$ para ambos). Não foram observadas diferenças significativas no tempo de imobilidade e escalada em todos os grupos ($p>0,05$). Por outro lado, os grupos RF e RP apresentaram redução do tempo gasto no centro da arena em comparação ao controle ($p<0,05$) no OFT, sugerindo aumento do comportamento semelhante à ansiedade. **Conclusão:** Nossos resultados mostram que a pregabalina tem um efeito agudo na depressão e também pode exercer de forma aguda um comportamento inesperado semelhante à ansiedade. Nosso trabalho revela um resultado inesperado na busca por antidepressivos de ação rápida.

Palavras-chave: Reserpina; pregabalina; depressão; ansiedade; modelo animal.

Introduction

Depression is a complex mood disorder shaped by an imbalance in the interaction between monoamine networks in the brain. Consequently, individuals struggling with depression tend to display behaviors of helplessness, negativity, and despair that ultimately impact their physical health as well. This disorder is characterized by changes

in appetite, abnormal social behavior, insomnia, fatigue, lack of energy, headaches, and inability to enjoy life [1]. Depression prevalence affects up to of 350 million people around the world; however, this condition has not yet been treated successfully due to the lack of effective therapeutic modalities and the social stigma that this entails [2].

One of the main reasons why depression remains poorly responsive to antidepressant treatment is its heterogeneous aetiology [3]. Studies have shown that close to 50% of depression cases are mediated by genes [4, 5]. This has provided a potential explanation for recurrent patients where vulnerability to depressive events constantly triggers the resurgence of the pathology. On the other hand, there are also clear sex differences [6]. Evidence has shown that women are 2-3 times more likely to develop Major Depressive Disorder (MDD) compared to men [7]. Even worse, it is the female sex who presents a greater severity of symptoms, greater functional impairment, more atypical depressive symptoms, and higher rates of comorbid anxiety [8, 9]. Recent investigations have evidenced the existence of denoted sexual dimorphism at the transcriptional level in MDD and highlight the importance of studying sex-specific treatments [6, 10, 11]. This clear evidence at the transcriptional level has not only shed new light on the understanding of the body's response to depression but has also helped explain the resistance to treatment present in many patients.

Through the last years depression symptoms have been largely associated with monoamine neurotransmitters. Among the main symptoms, sadness, appetite, aggression, suicidal ideation, guilt, and feelings of worthlessness are mainly associated with serotonin while motivation and sociability are dopamine-related. Moreover, it is important to note that many other symptoms are not caused by a single neurotransmitter, but rather the result of the interaction between them. This is the case of mood, sleep disturbances, psychomotor retardation, anhedonia, anxiety, fatigue and concentration deficiency that arise as a result of the imbalance between serotonin, dopamine and norepinephrine [12]. This central knowledge has dictated the path mainly used for the development of pharmacological treatments against depression in the last 30 decades.

Unfortunately, the current antidepressant treatments present drawbacks. People must wait at least 4 weeks before the treatment to produce significant results, meanwhile, they must also deal with the occurrence of side effects. Constipation, decreased vision, sexual dysfunction, high blood pressure, cognitive impairment, loss of libido, headache, agitation, and anxiety are just some of the most common reported after the use of monoamine modulators [13].

Interestingly, a recent study suggest that antiepileptic drugs, such as pregabalin, could ameliorate depressive symptoms [14]. Pregabalin is advised as first-line pharmacological agent for neuropathic pain [15], being intensely used for fibromyalgia syndrome

(FMS). Despite pregabalin prescriptions have increased over the last few years [16] yet our knowledge is still scarce about its potential application on mood disorders such as depression and anxiety. Initial investigations showed that while pregabalin significantly reduces the symptoms and side effects of many drug treatments, it does not have a significant effect in relieving depressive states [17-19]. Nevertheless, recent strong meta-analysis evidence has suggested a crucial role of pregabalin in the treatment of anxiety disorders [20], demonstrating its key influence in many of the most related symptoms and characteristics that also configure depression spectrum. Here, we evaluated the acute effects of pregabalin in a well stablished depression animal model induced by reserpine in rats.

Method

Animals

A total of twenty-four male adult Wistar rats of 3 – 4 months of age were purchased from "Instituto Nacional de Salud (INS)", Lima, Peru. Rats weighed in average between 300 – 400 g. The animals were housed in conventional plastic-steel cages in a 12 h light/dark cycle at room temperature of 22 ± 1 °C. Water and food were given *ad libitum* during all the procedures.

Experimental design

Upon arrival at our colony space, adult rats were randomly assigned to 4 groups (6 animals each) and acclimated for 5 days before experiments were performed. Groups were named regarding with planned drug regimen (Table 1): control (C) group, Reserpine (R) group, Reserpine + Pregabalin (RP), and Reserpine + Fluoxetine (RF).

Table 1. Drug regimen of the study

Groups	Number of Animals	Reserpinization (s)	Drug administration (o)
Control	6	Saline solution	Saline solution
Reserpine	6	1 mg/kg	Saline solution
Reserpine + Pregabalin	6	1 mg/kg	Pregabalin 30 mg/kg
Reserpine + Fluoxetine	6	1 mg/kg	Fluoxetine 10 mg/kg

Abbreviations: s: subcutaneous route; o: oral route. Saline solution was administrated subcutaneously in all cases.

On day 6, reserpine (Sigma-Aldrich, Buchs, Switzerland) was diluted in saline solution and administered subcutaneously (1 mg/kg) three consecutive days [14]. All animals received reserpine, except those in the C group. Two days after reserpinization, saline and treatments were administered orally (oral gavage technique). No fasting was required to proceed with oral gavage. RP mice was treated with pregabalin (Lyrica™; Pfizer, Madrid, Spain) with a single oral dose of 30 mg/kg [14], while the RF mice received fluoxetine (Prozac™, Eli Lilly Interamerica, Indianapolis, USA) in a single oral dose of 10 mg/kg [21, 22]. Behavioral assessment including forced swimming and open field testing were performed 2 hours after treatment administration. Finally, the animals were euthanized with two anesthetics: 100 mg/kg of ketamine and 10 mg/kg of xylazine injected intraperitoneally. Biological waste was discarded according to national policy following the 'Norma Tecnica de Salud' from the Peruvian Ministry of Health (NTSN°144-MINSA/2018/DIGESA). The experimental design is resumed in Figure 1.

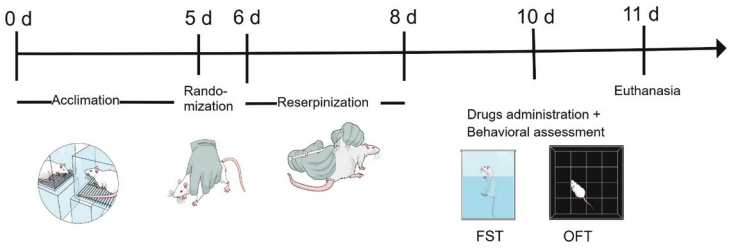

Figure 1. The experimental design for the study. Abbreviation: rand: randomization; FST: forced swimming test; OFT: Open field test.

Behavioural assessments

Forced swimming test (FST): 24 hours after the last reserpinization, all animals were individually placed for 5 minutes in a 23 litters glass cylinder of 34.1 cm in diameter and 38.1 cm in height, previously filled with water acclimated to 25 °C. This session prior to the test allows us to eliminate acute stress and the reaction to novelty in the animals, in addition to allowing them to know the challenging conditions of the task before their actual evaluation. One day after, the test was repeated rand immobility, climbing and swimming behaviors were evaluated during the first 3 minutes using a video camera located above the cylinder [23].

Open field test (OFT): animals were individually placed in the center of an arena (94 cm × 42 cm) and allowed to explore freely for 10 minutes. Total distanced travelled and velocity average were measured to study locomotor activity. On the other hand, the number of entrances to the center and time spent in the center were considered

to evaluate anxiety-like behavior [24]. The recordings were analysed using EthoVision video tracking software (Noldus, Leesburg, USA).

Statistical plan

All data were expressed as average ± standard deviation (SD). One-way analysis of variance (ANOVA), followed by Tukey *post-hoc* tests, were used with GraphPad Prism version 6 (GraphPad Software Inc., San Diego, CA, USA) to evaluate differences between groups. $p<0.05$ was considered statistically significant.

Ethical Considerations

All procedures were approved by "Comité Institucional de Ética para el Uso de Animales (CIEA)" de la Universidad Peruana Cayetano Heredia (UPCH), Lima, Peru (Protocol number 205561).

Results and discussion

Forced swimming test

We found significant differences between all groups in swimming time ($p=0.021$). *In* Tukey *post-hoc* test, RP and RF groups showed a longer swimming time compared to C group ($p=0.047$ and $p=0.037$, respectively). On the other hand, immobility and climbing time did not differ across all groups ($p>0.05$) (Figure 2).

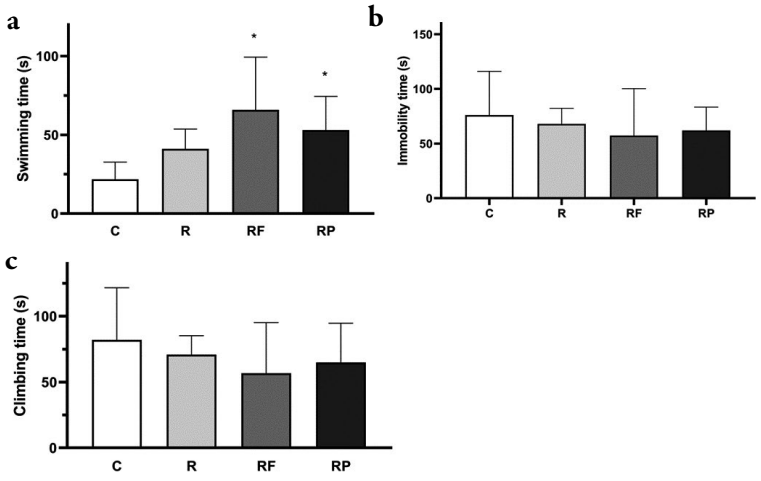

Figure 2. Effect of pregabalin and fluoxetine in reserpine pharmacological model. Forced swimming test: a) swimming time, b) immobility time, and c) climbing time. Bars represents mean ± SD. Legend: *$p<0.05$ in comparison to C group. ANOVA followed by Tukey *post-hoc* test.

Open Field Test

Regarding locomotor activity, we found differences in total distance travelled and average velocity during the test between all groups (p=0.003 for both). In Tukey *post-hoc* analysis, animals from RF and RP groups showed a lower traveled distance than C group (p=0.004 and p=0.022, respectively) and R group (p=0.001 and p=0.005, respectively). Similarly, RF and RP groups also displayed a reduction in average velocity in comparison that C group (p=0.004 and p=0.021, respectively) and R group (p=0.001 and p=0.006, respectively) (Figure 3).

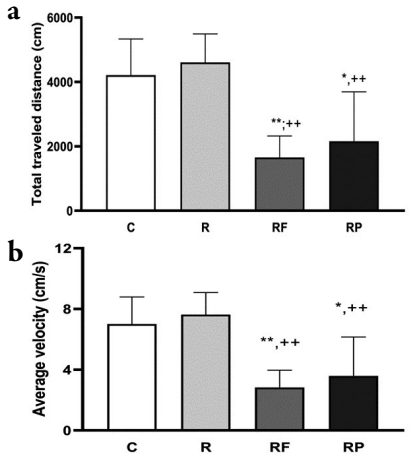

Figure 3. Effect of pregabalin and fluoxetine in reserpine pharmacological model. Open Field test (locomotor activity): a) total traveled distance, and b) average velocity. Bars represents mean ± SD. Bars represents mean ± SD. Legend: $^{**}p<0.001$ and $^{*}p<0.05$ in comparison to C group. $^{++}p<0.001$ in comparison to R group. ANOVA followed by Tukey *post-hoc* test.

In relation to anxiety-like behavior, all groups exhibited differences in the number of entrances to the center (p<0.0001) and the time spent in the center of the arena (p=0.002). In multiple comparison analysis, the RF and RP groups showed a reduction in the number of entrances to the center compared to control (p=0.0006 and p=0.0003, respectively) and the reserpine group (p=0.006 and p=0.0028, respectively). On the other hand, in another parameter, the RF and RP groups only displayed a decrease of time spent in the center with respect to the C group (p=0.006 and p=0.005, respectively, but not to the R group (p>0.05 for both) (Figure 4).

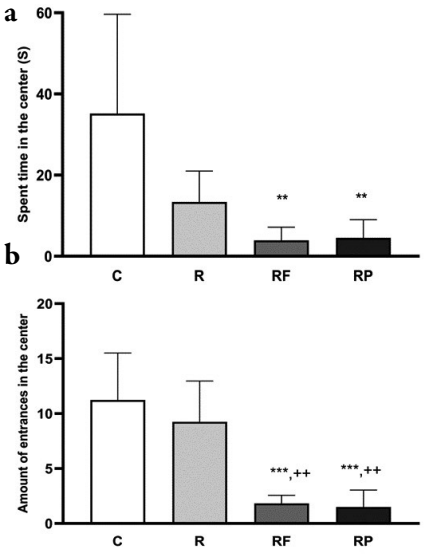

Figure 4. Effect of pregabalin and fluoxetine in reserpine pharmacological model. Open Field test (Anxiety-like behavior): a) spent time in the center, and b) amount of entrances in the center. Bars represents mean ± SD. Legend: ***p<0.0001 and **p<0.001 in comparison to C group. ++p<0.001 in comparison to R group. ANOVA followed by Tukey *post-hoc* test.

Major depression steadily increases in prevalence worldwide with more than 75% of the population from low- and middle-income countries without adequate treatment. A major barrier to treat patients with depression includes extant ineffective antidepressant drugs [25]. In this study, we set to investigate the acute effect of pregabalin in a rat model of reserpine-induced depression using the FST and OFT.

Molecularly, reserpine-induced depression may stem from the irreversible inhibition of the vesicular monoamine transporter 2 receptor leading to leakage and degradation of biogenic amines stored in pre-synaptic vesicles [26]. The degradation of these amines includes neurotransmitters such as serotonin, dopamine and norepinephrine and causes depletion of transmitters at pre-synaptic terminals.

Serotonin has been implicated in depression for decades due to the pharmacological properties of antidepressants such as fluoxetine [27]. The FST was developed to test depressive-like states and the well-characterized effects of fluoxetine on this behavioral assay provides a proxy to serotonin involvement.

In the FST, we only observed longer swimming time in the RP and RF group compared to C group. Notably, pregabalin mimicked fluoxetine antidepressant effect as swimming time in both groups were similar. Even though the R group did not show the expected behavior in this test, we attribute it to inter-strain variability, animal age, and reserpine dose.

We followed González-Soler's protocol [14] to acutely induce depressive-like behavior using a 3-consecutive day regime of 1 mg/kg reserpine subcutaneously on male Sprague-Dawley rats. On her study, it is possible to assume that rats showed depressive-like behavior because duloxetine improved swimming time and reduced immobility time; however, the authors did not show a vehicle group without reserpine to set a baseline level for the forced swimming test. Even though it has been shown that acute administration of reserpine can induce depressive-like behavior using appropriate control groups [28], we speculate that 1 mg/kg of reserpine for 3 consecutive days may not exert a profound impact on learned hopelessness on the FST compared to no reserpine. The acute administration of reserpine in adult Wistar rats may differently affect depressive-like and anxiety-like behaviors with certain degree of variability. This variability can depend on the susceptibility of rats to reserpine due to maturation of brain circuitry. For instance, Ruiz et al. has recently explored the effects of reserpine-induced depression and fluoxetine on adolescent alcohol intake [29]. They showed that 1 mg/kg of reserpine for 4 days drove depressive-like behaviors on adolescent post-weaned 1 month-old male and female Wistar rats.

The effect of reserpine may be affected by dose. Ahmed and col. used a high-dose of reserpine to induce depressive-like behaviors acutely in adult male Wistar rats [30]. In the study, rats receiving reserpine intraperitoneally 6 mg/kg showed a significant increase in immobility time in the forced swimming test compared to control, 1 day after the injection. Another study that aimed to use a reserpine-induced model of depression also showed acute depressive-like behaviors only 1-hour post-injection with reserpine doses from 4 to 8 mg/kg [28].

Ahmed *et al.* [30] showed that fluoxetine administered for 3 days after reserpinization restored immobility time suggesting that this drug can acutely display antidepressant effects. Despite the paradoxical effect of reserpine in the FST, the intervention with fluoxetine and pregabalin acted on learned helplessness and behavioral despair. To extensively dissect the effects of reserpine and pregabalin, we recommend coupling behavioral analysis to molecular correlates.

Given the dopamine depleting effects of reserpine and the known co-morbidity of depression and anxiety, we extended our analysis to the open field test. Reserpine

at 1 mg/kg dose in our study did not reduce overall traveled distance or speed suggesting that dopamine signaling still acts to perform motor activity primarily via striatum [31]. In addition, no significant effects were observed in the time spent at the center between the R and C groups strengthening the notion that lack of complete dopamine depletion may explain no notable effects on anxiety-like behaviors. Interestingly, acute treatment with pregabalin in our model exerted an unexpected anxiogenic effect.

In the study of Ruiz *et al.* [29], they showed that 4 consecutive doses of reserpine at 1 mg/kg reduced travelled distance and reduced the time spent in the center of the open field chamber. The levels of dopamine in the insular cortex were also reduced pointing out that lack of dopamine signaling could explain locomotor deficits and anxiogenic behavior [29]. In the work of Ahmed *et al.* [30], the lack of overall motor activity could be explained by ablation of dopaminergic signaling due to high-dose reserpine (6 mg/kg). The reason for the lack of effect on anxiety-like behaviors in the reserpine group may lie on remaining dopaminergic signaling.

High doses of fluoxetine administered acutely may also have a sedative effect reducing locomotor activity shown in the elevated plus-maze test [32]. This also explains the reduced activity in our study. We need to note that pregabalin shows a similar effect as acute fluoxetine treatment increases anxiety-like behavior. Even though both drugs act on different targets, acute pharmacological effect may converge in the nucleus for motor and anxiety control.

Our limitations in this work were related to the lack of molecular, histological, and electrophysiological studies, which would offer more information about potential targets or molecule that could explain these outcomes. Another limitation was that we cannot observed differences in depressive or anxiety-like behavior between R and C group. This fact could be explained because reserpine acts on multiple pathways and not only those related to depression [33].

Our results suggests that acute pregabalin administration can ameliorate depressive-like behavior in a pharmacological model in rats. This could be explained by an acute action on 5-HT, DA, NA or GABA system. However, further studies are needed in order to confirm these results and elucidate monoaminergic pathways that could participate in this process.

Conflicts of interest

The authors declare no conflict of interest.

References

1. K. Smith, Mental health: A world of depression, *Nature*, **515**, 180–181 (2014).

2. C. Otte, S.M. Gold, B.W. Penninx, C.M. Pariante, A. Etkin, M. Fava, D.C. Mohr, A.F. Schatzberg, Major depressive disorder, *Nat. Rev. Dis. Prim.*, **2**, 16065 (2016).

3. R.H. Belmaker, G. Agam, Major depressive disorder, *N. Engl. J. Med.*, **358**, 55–68 (2008).

4. B.D. Hare, R.S. Duman, Prefrontal cortex circuits in depression and anxiety: Contribution of discrete neuronal populations and target regions, *Mol. Psychiatry*, **25**, 2742–2758 (2020).

5. J. Flint, K.S. Kendler, The genetics of major depression, *Neuron*, **81**, 484–503 (2014).

6. B. Labonté, O. Engmann, I. Purushothaman, C. Menard, J. Wang, C. Tan, J.R. Scarpa, *et al.*, Sex-specific transcriptional signatures in human depression, *Nat. Med.*, **23**, 1102–1111 (2017).

7. R.C. Kessler, W.T. Chiu, O. Demler, K.R. Merikangas, E.E. Walters, Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication, *Arch. Gen. Psychiatry*, **62**, 617–627 (2005).

8. S.G. Kornstein, A.F. Schatzberg, M.E. Thase, K.A. Yonkers, J.P. McCullough, G.I. Keitner, *et al.*, Gender differences in chronic major and double depression, *J. Affect. Disord.*, **60**, 1–11 (2000).

9. R.C. Kessler, K.A. McGonagle, M. Swartz, D.G. Blazer, C.B. Nelson, Sex and depression in the National Comorbidity Survey I: Lifetime prevalence, chronicity and recurrence, *J. Affect. Disord.*, **29**, 85–96 (1993).

10. M. Touchant, B. Labonté, Sex-specific brain transcriptional signatures in human MDD and their correlates in mouse models of depression, *Front. Behav. Neurosci.*, **16**, 845491 (2022).

11. M. Maitra, H. Mitsuhashi, R. Rahimian, A. Chawla, J. Yang, L.M. Fiori, *et al.*, Cell type specific transcriptomic differences in depression show similar patterns between males and females but implicate distinct cell types and genes, *Nat. Commun.*, **14**, 2912 (2023).

12. E. Beurel, M. Toups, C.B. Nemeroff, The bidirectional relationship of depression and inflammation: Double trouble, *Neuron*, **107**, 234–256 (2020).

13. S. Marwaha, E. Palmer, T. Suppes, E. Cons, A.H. Young, R. Upthegrove, Novel and emerging treatments for major depression, *Lancet*, **401**, 141–153 (2023).

14. E.M. González-Soler, A. Blasco-Serra, G.M. Alfosea-Cuadrado, M. Igual-López, J. Orduña-Valls, C. Tornero-Tornero, *et al.*, Chronic pregabalin treatment ameliorates pain, but not depressive-like behaviors, in a reserpine-induced myalgia model in rats, *Pain Physician*, **23**, E581–E590 (2020).

15. Y. Wang, H. Yang, C. Shen, J. Luo, Morphine and pregabalin in the treatment of neuropathic pain, *Exp. Ther. Med.*, **13**, 1393–1397 (2017).

16. I.J. Onakpoya, E.T. Thomas, J.J. Lee, B. Goldacre, C.J. Heneghan, Benefits and harms of pregabalin in the management of neuropathic pain: A rapid review and meta-analysis of randomised clinical trials, *BMJ Open*, **9**, e023600 (2019).

17. W. Häuser, F. Petzke, N. Üçeyler, C. Sommer, Comparative efficacy and acceptability of amitriptyline, duloxetine and milnacipran in fibromyalgia syndrome: A systematic review with meta-analysis, *Rheumatology* (Oxford), **50**, 532–543 (2011).

18. S. Quilici, J. Chancellor, M. Löthgren, D. Simon, G. Said, T.K. Le, A. Garcia-Cebrian, B. Monz, Meta-analysis of duloxetine vs pregabalin and gabapentin in the treatment of diabetic peripheral neuropathic pain, *BMC Neurol.*, **9**, 6 (2009).

19. W. Häuser, F. Petzke, C. Sommer, Comparative efficacy and harms of duloxetine, milnacipran, and pregabalin in fibromyalgia syndrome, *J. Pain*, **11**, 505–521 (2010).

20. M.B. Generoso, A.P. Trevizol, S. Kasper, H.J. Cho, Q. Cordeiro, P. Shiozawa, Pregabalin for generalized anxiety disorder: An updated systematic review and meta-analysis, *Int. Clin. Psychopharmacol.*, **32**, 49–55 (2017).

21. S. Jayakumar, G. Raghunath, S. Ilango, J. Vijayakumar, R. Vijayaraghavan, Effect of fluoxetine on the hippocampus of wistar albino rats in cold restraint stress model, *J. Clin. Diagnostic Res.*, **11**, AF01–AF06 (2017).

22. S.C. Dulawa, K.A. Holick, B. Gundersen, R. Hen, Effects of chronic fluoxetine in animal models of anxiety and depression, *Neuropsychopharmacology*, **29**, 1321–1330 (2004).

23. D. Kuzay, E. Dileköz, Ç. Özer, Effects of thymoquinone in a rat model of reserpine-induced depression, *Braz. J. Pharm. Sci.*, **58**, e19847 (2022).

24. K.R. Lezak, G. Missig, W.A. Carlezon, Behavioral methods to study anxiety in rodents, *Dialogues Clin. Neurosci.*, **19**, 181-191 (2017).

25. F.C. Gabriel, D.O. de Melo, R. Fráguas, N.C. Leite-Santos, R.A. Mantovani da Silva, E. Ribeiro, Pharmacological treatment of depression: A systematic review comparing clinical practice guideline recommendations, *PLoS One*, **15**, e0231700 (2020).

26. T. Hedgecock, A. Phillips, B. Ludrick, T. Golden, N. Wu, Molecular mechanisms and applications of a reserpine-induced rodent model, *SSR Inst. Int. J. Life Sci*., **5**, 2160–2167 (2019).

27. J. Moncrieff, R.E. Cooper, T. Stockmann, S. Amendola, M.P. Hengartner, M.A. Horowitz, The serotonin theory of depression: A systematic umbrella review of the evidence, *Mol. Psychiatry*, **28**, 3243–3256 (2023).

28. Q. Huang, H. Jiang, X. Hao, T.R. Minor, Brain IL-1 beta was involved in reserpine-induced behavioral depression in rats, *Acta Pharmacol. Sin.*, **25**, 293–296 (2004).

29. P. Ruiz, A. Calliari, R.M. Pautassi, Reserpine-induced depression is associated in female, but not in male, adolescent rats with heightened, fluoxetine-sensitive, ethanol consumption, *Behav. Brain Res.*, **348**, 160–170 (2018).

30. R.F. Ahmed, R.F. Abdel-Rahman, O.A.H.A. Farid, S.A. El-Marasy, A.F. Hessin, Combined hepatoprotective and antidepressant effects of resveratrol in an acute model of depression, *Bull. Fac. Pharm.*, *Cairo Univ.*, **52**, 191–197 (2014).

31. Y. Li, Q. Yin, B. Wang, T. Shen, W. Luo, T. Liu, Preclinical reserpine models recapitulating motor and non-motor features of Parkinson's disease: Roles of epigenetic upregulation of alpha-synuclein and autophagy impairment, *Front. Pharmacol.*, **13**, 944376 (2022)

32. D. Drapier, D. Bentué-Ferrer, B. Laviolle, B. Millet, H. Allain, M. Bourin, J.M. Reymann, Effects of acute fluoxetine, paroxetine and desipramine on rats tested on the elevated plus-maze, *Behav. Brain Res.*, **176**, 202–209 (2007).

33. M. Cheung, M. Parmar, Reserpine, StatPearls [Internet]. URL: https://www.ncbi.nlm.nih.gov/books/NBK557767/, accessed September **1**, 2023.

How to cite this article

A. Casas-Lucich, A.B. Campos-Salazar, V. Vasquez-Matsuda, J. Salvador-Carrillo, G. Ojeda-Mercado, Acute effect of pregabalin on depressive- and anxiety-like behaviors in adult rats in a pharmacologic model of depression, *Rev. Colomb. Cienc. Quim. Farm.*, **52**(3), 1406-1420 (2023). https://doi.org/10.15446/rcciquifa.v52n3.111080